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TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US)

10/089663

INTERNATIONAL APPLICATION NO. PCT/EP00/09558	INTERNATIONAL FILING DATE September 29, 2000	PRIORITY DATE CLAIMED October 1, 1999

TITLE OF INVENTION

BIODEGRADABLE EXCIPIENT SYSTEMS FOR THERAPEUTICALLY ACTIVE SUBSTANCES AND METHOD FOR PRODUCING THE SAME

APPLICANT(S) FOR DO/EO/US

Armin PRASCH and Bernhard LUY

Applicant herewith submits to the United States Designated/Elected office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.

2. [] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.

3. [] This is an express request to begin national examination procedures (35 U.S.C. 371 (f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S. C. 371 (b) and PCT Articles 22 and 39 (1).

4. [X] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. [X] A copy of the International Application as filed (35 U.S. C. 371 (c) (2))
   a. [] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [X] has been transmitted by the International Bureau
   c. [] is not required, as the application was filed in the United States Receiving Office (RO/US)

6. [X] A translation of the International Application into English (35 U.S. C. 371 (c)2)).

7. [X] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. [] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [] have been transmitted by the International Bureau.
   c. [] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [X] have not been made and will not be made.

8. [] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c) (3)).

9. [X] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).

10. [] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. [] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.

12. [] An assignment document for recording. A **separate** cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. [X] A FIRST preliminary amendment.
    [] A SECOND or SUBSEQUENT preliminary amendment.

14. [] A substitute specification.

15. [] A change of power of attorney an/or address letter.

16. [X] Other items or information: English Translation of Claims 1-15, as amended under PCT Article 34 on November 13, 2001

EXPRESS MAIL CERTIFICATE

3/29/02 Date EV039140715US Label No.

I hereby certify that on the date indicated above, this paper or fee was deposited with the U.S. Postal Service & that it was addressed for delivery to the Assistant Commissioner for Patents, Washington, DC 20231 by "Express Mail Post Office to Addressee" service.

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Name (Print) Signature

U.S. APPLICATION NO. (if known, see 37 C.F.R. 1.50)	INTERNATIONAL APPLICATION NO.: PCT/EP01/06298	Attorney's Docket Number 3671/0K437
10/089663		

17. [x] The following fees are submitted:	CALCULATIONS	PTO USE ONLY
Basic National Fee (37 CFR 1.492 (a)(1)-(5)): Search Report has been prepared by the EPO [X] or JPO [] **$890.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.482) **$710.00**		
No international preliminary examination fee paid to USPTO(37 CFR 4.482) but international search fee paid to USPTO (37 CFR 1.445 (a) (2)... **$740.00**		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO..... **$1,040.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4).... **$100.00**		
= **ENTER APPROPRIATE BASIC FEE AMOUNT** =	$890.00	
Surcharge of $130.00 for furnishing the oath or declaration later than []20 []30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

Claims	Number Filed	Number Extra	Rate		
Total Claims	**17-20**	0	X $18.00	**$0.00**	
Independent Claims	**1-3**	~~$0~~	X $80.00	~~$~~0.00	
Multiple dependent claims(s) (if applicable)		+280		$280.00	
			TOTAL OF ABOVE CALCULATIONS =	**$1,1700.00**	
Reduction by 1/2 for filing by small entity, if applicable.				**$1,170.00**	
			SUBTOTAL =	**$1,170.00**	
Processing fee of **$130.00** for furnishing the English translation later the [] 20 [] 39 months from the earliest claimed priority date (37 CFR 1.492(f)).			+	$	
			TOTAL NATIONAL FEE =	**$1,170.00**	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). the assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property			+	$0.00	
			TOTAL FEES ENCLOSED =	**$1,170.00**	
				Amount to be refunded	$
				charged	$

a. [X] A check in the amount of $**1,170.00** to cover the above fees is enclosed.

b. [] Please charge my Deposit Account No.04-0100 in the amount of $ to cover the above fees.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 04-0100. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO

Michael J. Sweedler
Darby & Darby P.C.
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New York, New York 10150-5257

SIGNATURE _____

NAME Irina E. Vainberg, Ph.D.

REGISTRATION NO 48,008

EXPRESS MAIL CERTIFICATE

Date 3/29/02 Label No. EV 039140715US

I hereby certify that, on the date indicated above, this paper or fee was deposited with the U.S. Postal Service & that it was addressed for delivery to the Assistant Commissioner for Patents, Washington, DC 20231 by "Express Mail Post Office to Addressee" service.

D B Peck

Name (Print)

Signature

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Customer No.: 07278

PATENT TRADEMARK OFFICE

Docket No: 3671/0K437

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Armin PRASCH and Bernhard LUY

Serial No: TO BE ASSIGNED

Filed: CONCURRENTLY

For: BIODEGRADABLE EXCIPIENT SYSTEMS FOR THERAPEUTICALLY ACTIVE SUBSTANCES AND METHOD FOR PRODUCING SAME

National Phase of International Patent Application Serial No. PCT/EP00/09558, filed September 29, 2000

PRELIMINARY AMENDMENT

Hon. Commissioner of
Patents and Trademarks
Washington, DC 20231

Sir:

Prior to examination, please amend the above-identified application as follows:

IN THE CLAIMS:

Please amend the claims pursuant to 37 C.F.R. §1.121 as follows:

Cancel claims 1-17 without prejudice and substitute therefor:

18. (New) A biodegradable depot medicament formulation comprising:

(i) a carrier system comprising a biodegradable blood plasma protein, which has been dried by fluidized bed drying with retention of its properties, wherein said blood plasma protein is selected from the group consisting of thrombin, fibrinogen, albumin, and mixtures thereof, and wherein the carrier system is in the form of microporous granules with a particle size in the range from 20 to 500 μm, and

(ii) an active ingredient, which is to be administered as a depot or as an active ingredient combination.

19. (New) The depot medicament formulation of claim 18, wherein the carrier system is a solid which has been produced by compression of the granules.

20. (New) The depot medicament formulation of claim 18, characterized in that it is in the form of a granule mixture of particles of the carrier system and of the active ingredient.

21. (New) The depot medicament formulation of claim 18, characterized in that it is in the form of mixed granules of the biodegradable blood plasma protein and of the active ingredient or of the active ingredient combination thereof.

22. (New) The depot medicament formulation of claim 18, characterized in that it is composed of mixtures of particles or granules which are formed of an internal core and an external layer, wherein the external layer has been formed by the blood plasma protein, and the internal core comprises an inert excipient.

23. (New) The depot medicament formulation of claim 22, wherein the inert excipient is a carbohydrate selected from the group consisting of lactose and mannitol.

24. (New) The depot medicament formulation of claim 18, characterized in that it is in the form of compact homogeneous micropellets with an average particle diameter in the range from 35 to 500 μm.

25. (New) The depot medicament formulation of claim 24, wherein the average particle diameter is in the range from 50 to 150 μm.

26. (New) The depot medicament formulation of claim 18, characterized in that it comprises ceramic granules, or calcium phosphates, or both, which have been compressed together to give a shaped article and which have then been coated with the blood plasma protein.

27. (New) The depot medicament formulation of claim 26, wherein the blood plasma protein coating further comprises antibiotics, or growth factors, or both.

28. (New) The depot medicament formulation of claim 18 or 27, wherein the active ingredient is selected from the group consisting of antibiotics,

corticosteroids, antimycotics, neuroleptics, antiepileptics, steroid hormones, anticancer hormones, substances which promote wound healing, cytostatics, immunomodulators, anesthetics, analgesics, peptide hormones, antirheumatics, vaccines, antibodies, nucleic acids, peptides, proteins, growth factors, cells, and combinations thereof.

29. (New) The depot medicament formulation of claim 18, characterized in that it is employed for topical administration.

30. (New) The depot medicament formulation of claim 18, characterized in that it is employed for parenteral administration.

31. (New) The depot medicament formulation of claim 18, characterized in that it is employed for transdermal administration.

32. (New) The depot medicament formulation of claim 26 or 27, characterized in that it is employed as an implant.

33. (New) The depot medicament formulation of claim 32, wherein the implant is a bone replacement.

34. (New) A process for producing the depot medicament formulation of claim 18 comprising:

(i) spraying the biodegradable blood plasma protein in the form of a solution, or suspension, or both into a fluidized bed installation, and

(ii) drying under mild conditions with retention of the properties.

REMARKS

Claims 1-17 of the PCT application Serial No. PCT/EP00/09558 (as presented in the English translation filed herewith) have been cancelled and rewritten as new claims 18-34 to be placed in better form for U.S. patent practice, including the removal of improper multiple dependent claims.

This amendment was not made for matters affecting patentability of the claims. No new subject matter has been incorporated into the application as a result of this amendment.

Entry of the above amendment is respectfully requested prior to the examination of this application.

Following entry of the amendment, claims 18-34 are presented for examination in this case. Favorable consideration and an early action on the merits is respectfully requested.

The Examiner is hereby authorized to charge any additional fees associated with this submission to our Deposit Account No. 04-0100.

Respectfully submitted,

Dated: March 29, 2001

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Biodegradable carrier systems for therapeutically active substances and process for their production

The invention relates to a suitable formulation of a biodegradable carrier system for therapeutically active pharmaceutical substances which on the one hand promote wound healing or which are able specifically to have additional pharmacological effects in the organism. Release of the active ingredient is intended with the described drug forms to take place in a delayed and gradual manner, resulting in a prolonged action for these drug forms in the sense of a depot. The carrier systems are biodegradable polymers which are toxicologically acceptable, tolerable and immunogenic in the human or veterinary organism. Blood plasma proteins, in particular fibrin glue components fibrinogen and thrombin are employed according to the invention. Production takes place by a granulation or spray agglomeration process in a fluidized bed, which makes it possible to adjust specific product properties.

Fibrin glues or tissue glues are employed in human medicine and in certain cases (e.g. race horses) also in veterinary medicine usually for example in surgical operations to promote blood coagulation or hemostasis and for closing wounds. The principle of fibrin gluing corresponds to the last stage of the natural hemostasis system in mammals, a coenzyme/enzyme controlled cascade reaction in which fibrinogen is converted by thrombin in the presence of factor XIII and Ca^{2+} ions into fibrin. During wound healing, the fibrin is broken down again by proteolysis and thus absorbed in a natural way. Technically, the principle of operation of the fibrin glues resembles the principle of two-component or multicomponent adhesives which are mixed together or brought into contact usually either only at the place which is to be bonded or else only shortly before the

actual time.

Care must be taken on administration and use of fibrin tissue glue that fibrinogen and thrombin are brought together only at the immediate site of the bleeding, because the onset of coagulation is spontaneous. Adjacent sites must moreover be well covered because of the very good adhesive effect. A precondition for the coagulation is free mobility of the individual molecules involved, for example in water. This is usually achieved in practice by separating the two crucial components fibrinogen and thrombin until applied to the wound, bringing them into contact with one another only directly on the wound.

The components must each be packaged sterile and stored in a suitable form and under defined conditions so that the activity of the individual proteins or enzymes is not harmed by the storage. This is usually achieved by the protein concentrates being present in freeze-dried form in vials. In this form they are stable on storage under refrigerator conditions (4 to 8°C) for a defined time, and even under ambient conditions (20°C) for a shorter time. However, freeze-dried, the concentrate is in solid, compressed and thus immobile form, but in the form of a soluble solid. It is therefore necessary for the protein concentrates to be completely redissolved before use in order to be able to start the desired biochemical reaction. As an alternative to this it is possible for the components also to be stored stably in a deep-frozen solid form, and they must then be thawed before use and be applied separately as solution.

The two solutions can then in each case be brought together by syringes, for example in the same ratio by volume. In this case, the fibrinogen solution must be applied to the wound first and be covered as quickly as possible with a layer of the thrombin solution. The parts to be glued must then be immobilized until a

preliminary uniting has occurred.

In addition, the patent application WO 97/44015 describes the production of microparticles based on fibrinogen and thrombin, each of which are spray-dried separately. The removal of water associated with this reduces the mobility of the protein molecules so far that the onset of coagulation cannot occur spontaneously. The microparticles are all smaller than 20 µm, preferably smaller than 10 µm or 2-5 µm, and are said to be readily soluble. Mixed together, these fibrinogen- and thrombin-containing microparticles can be employed for hemostasis. However, one disadvantage is that much dust is associated with the powder, making direct application virtually impossible.

Fibrin glues of human, animal or else recombinant origin are characterized by immediate and comparatively strong adhesion at the site of application (e.g. wound, tissue) of the fibrin formed, the matrix structure which forms in the crosslinked fibrin, and the spontaneous biodegradability of the fibrin. The natural components are additionally distinguished in that these components are already present in the human or else animal organism and therefore are toxicologically acceptable and well tolerated.

Because of these characteristics (adhesion, matrix structure, tolerability and degradability), fibrin glues or components of a fibrin glue may be a suitable carrier system for additional therapeutically active substances. Since, however, a fibrin glue can, as described, be applied only as solution or in two separate solutions, it is problematic to construct homogeneous release-controlling matrix structures for active ingredient-containing fibrin glue formulations.

A number of publications have disclosed fibrin glues as

carriers of active ingredients. Besides the use of antibiotics for suppressing local infections, there have also been addition of cytostatics to fibrin glues for local chemotherapeutic treatment for example of remaining cancer cells after surgical removal of the primary tumor. Zinc, for example, has also been incorporated into fibrin glues in order thus to achieve a higher content of zinc over a prolonged period directly in the wound and thus make improved wound healing possible (US 6,651,982). In addition, EP 804153A1 also describes the combination of a fibrin glue with a therapeutic active ingredient which can be employed, for example, after surgical removal of a tumor, as radiotherapeutic active ingredient.

It is thus known that fibrin glues can be employed as carrier system for therapeutic active ingredients. It is possible by suitable measures to control active ingredient release in such a way that the release takes place in a delayed fashion over a defined period. The release of these active ingredients from the fibrin glue carrier system varies from 24 hours to a number of days according to the statements in the scientific literature; the release of slightly soluble active ingredients may in fact last for up to 40 days. It is accordingly possible by combining a fibrin glue with therapeutically active substances also to achieve a delayed or extended release of active ingredient with a slow, constant uptake of active ingredient into the blood stream and thus a constant concentration level of the active ingredient in the blood.

Dosage forms of this type are generally known under the name depot drug forms and are the aim of numerous developments. Depot drug forms are also used parenterally. The advantage which emerges in this case is, for example, that depot drug forms with delayed release can be administered to patients instead of a

continuous i.v. infusion, which means considerably greater independence and mobility for the patient. This may also make it possible by targeted local administration and, resulting therefrom, local release of active ingredient for substances such as highly active substances such as, for example, cytostatics or else particular antibiotics to be employed in a more targeted manner and thus in lower dosage than when they display a systemic action affecting the whole organism via the usual route of oral administration. In summary it can be stated that the scientific literature shows that fibrin glues have a good potential as carrier system both for hydrophilic and for lipophilic active ingredients, with a delayed release profile.

Known parenteral depot drug forms are

- Aqueous suspensions for slightly soluble active ingredients by subcutaneous or intramuscular injections. Example: insulin products (duration of action 12-36 h). The very elaborate aseptic method of manufacture of parenteral suspensions is characteristic.

- Oily solutions, suspensions: active ingredient dissolved or suspended in oil, whereby absortion of the active ingredient in the aqueous phase of the tissue (and thus the therapeutic active ingredient release) is intended or retarded. Products are in some cases marked by a very long duration of action (weeks to months).

- Emulsions: after subcutaneous or intramuscular injection, emulsions are distributed in the tissue and are absorbed there. Systems of this type are currently still characterized by a high degree of incompatibility.

[redacted]

- Highly viscous solutions, suspensions, hydrocolloids (polyvidone, cellulose derivatives), in particular for protein and peptide active ingredients (simultaneously protective colloid effect and suspension stabilizers).
- Use of particulate vehicles - microparticles, liposomes, implants. Microparticles and liposomes appear macroscopically as suspension and dispersion respectively. Implants are, by contrast, solids and are used as such. The first products of this type have been launched in various countries. Besides the nondegradable silicon implants which, after delivery of the embedded active ingredient, must be removed again by a minor surgical operation, the advantage of particulate vehicles is that they are biodegradable and thus are removed completely from the tissue after their hydrolytical cleavage by the organism itself. It should be noted that the resulting degradation products must not be either toxic or immunogenic, or carcinogenic. The polymers which are mostly used are therefore produced from tissue-compatible lactic acid and glycolic acid monomers (PLGA). However, albumin microparticles are also known in radiodiagnosis and are very suitable in particular because of their good tolerability and biodegradability. The like may also apply to particulate vehicles composed of fibrin glue components.

It is common to the technical solutions for the manufacture of parenteral depot drug forms by use of dissolved, suspended or emulsified active ingredients in water, solvent or oil that the methods of manufacture involved are always very elaborate and, in particular, in some cases the administrations are also complicated and their pharmacological action can be displayed only after a number of (bio)chemical/physical absorption, transport or dissolution processes in the

organism. A result of this is that the actual bioavailability can be controlled and monitored to only a limited extent.

It would therefore be an advantageous development to find for such carrier systems (which have to date been administered as liquids) a dosage form which is characterized by a defined matrix structure which remains constant or is gradually degraded during the administration for the duration of the desired release of active ingredient. These are properties which have already been realized for example for certain solid pharmaceutical dosage forms (such as tablets) which have a defined, delayed release behavior for example in the gastrointestinal tract. This cannot be realized with liquid administrations as are at present usual for fibrin glue components. Such novel dosage forms ought to be improved depot drug forms.

On the other hand, it appears advantageous to use particulate vehicles which can in some circumstances be employed directly at the site of action as long as they can be immobilized there in a suitable way. The release of active ingredient then takes place for example by diffusion-controlled absorption in the tissue or at the site of action. Administration might in this case advantageously take place directly for example as dry powder without the microparticles being suspended in a carrier liquid. Direct dry administration by injection of the dry particles can take place for example with the aid of PowderJect® technology ("needle-free injection"). Suitable particle sizes for this method are between 50 and 200 µm. It is also possible to inject smaller particles as suspension or to implant larger shaped articles with a larger needle suitable for this purpose.

The microparticles are produced either by phase

separation methods or by spray drying a polymer/active ingredient solution or suspension. It is likewise required that the production conditions are sterile or at least aseptic, which is very demanding. This requirement is usually avoided by sterilizing the microparticles after the spray drying. However, this procedure can be applied for example only to synthetic polymers which do not undergo unwanted changes in the sterilization process. Thermally labile biological polymers with protein-based specific activity, such as, for example, fibrin glues and fibrinogen, may in some circumstances be denatured by such a treatment, and thus this method is unsuitable for polymers of this type. In addition, spray-dried particles are also in particular characterized in that the particle sizes are very small (usually < 20 µm) and thus are very prone to dusting and are not free-flowing in practice, which greatly restricts accurate metering and direct application of the solid powder.

In the scientific literature there is a description by Senderoff et al. of the use of fibrin glues as carrier system for therapeutically active components based on microparticles, and in this case the proposed systems are fibrin glues as microparticles, fibrin glue particles with sugar coating and fibrin glue strips with dispersed active ingredient particles. Microparticles can be obtained after preceding emulsification of the active ingredient, extraction with an organic solvent and subsequent evaporation of the solvent. Especially when these production steps must be carried under aseptic conditions on the industrial scale, the process is made very elaborate thereby and is to be regarded as very problematic from the industrial viewpoint.

The object thus is to produce solid particles in a suitable manner that they can be employed as carrier

systems for therapeutically active substances, and can also at the same time be administered as solid. The components forming the carrier system are essentially biodegradable blood plasma proteins which may comprise, for example, at least one fibrin glue component. However, other human or animal proteins may also be suitable, such as, for example, albumin, which is distinguished in that albumin already has an important biochemical transport function in the organism and is therefore both well tolerated and degradable.

This is achieved by the invention in that particles which comprise, for example, the components fibrinogen and thrombin are produced in a granulation process in a fluidized bed. The procedure for this is analogous to the process described in German application 198 49 589.7, in which either mixed granules comprising at least fibrinogen and thrombin or else granule mixtures which represent a mixture of fibrinogen- and thrombin-containing granules, are produced in a fluidized bed process. Besides the fibrin glue components, it is also possible to apply one or else a plurality of additional therapeutic pharmacological active ingredient component(s) to the particle or the granules so that they are sufficiently immobilized there in order to make administration together with the fibrin glue components possible. This can usually take place in fluidized bed applications by spraying the additional active ingredient together with at least one of the fibrin glue components, preferably with fibrinogen or else with thrombin, simultaneously from a polymer/active ingredient solution or suspension, or else by spraying the active ingredient subsequently from a polymer/active ingredient solution or suspension onto the granules which comprise both fibrinogen and thrombin. In the first variant, the active ingredient can, for example, be integrated directly into the interior of the granules into the solid fibrin glue

matrix, while in the second variant the active ingredient or the active ingredients can be bound to the surface of the particles or granules. Moreover the additional process options known for fluidized bed processes, such as application of a (protective) coating consisting of a coating material or else of a colloid (polyvidone or cellulose derivatives), are possible. These coatings can be applied for example inside the granule as separating layers or only as pure external coating on the surface. The purpose of these coatings may be to achieve a protection for example of the active ingredient (for example for coating with antioxidants in the case of oxidation-sensitive active ingredients) or else to alter (extend) the delayed release of active ingredient. However, it must be noted in this connection that possible external coatings may presumably also reduce or, in some circumstances, also enhance the adhesive effect of the fibrin glue. A coating composed of molecules with a particular affinity for particular tissues is also conceivable. Besides the fibrin glue components as carrier polymer it is also possible in an analogous procedure to produce granules or powders composed of albumin or of the biodegradable proteins mentioned.

In this connection too it is necessary to observe very strict manufacturing instructions for products employed parenterally, in particular concerning rigorous conformance of all process and technical measures with maximum microbiological cleanliness. Both sterile (aseptic) filling, especially of temperature-sensitive preparations which cannot be sterilized in the final container, and the requirement for lower initial microbe counts make it obligatory to employ optimal cleanliness and appropriately developed (aseptic) production lines.

It is proposed, as shown in fig. 1, that the principal

production steps for isolating and obtaining the polymers (e.g. the blood plasma protein fractions fibrinogen and thrombin) and the active ingredients, and the production of the powder or of the granules or of the micropellets and the filling of the granules into the final packaging be separated. In this connection it is possible, depending on requirements, to comply appropriately with the particular room classes (clean room zone A and room zone C/D) required by national and international guidelines (for example GMP guidelines).

The requirement for the area of production of the granules or powders or pellets (fig. 2) is - as usual in pharmaceutical production - that the production area and technical area are clearly spatially separate from one another, e.g. through constructional measures 38. Located in the technical area are the necessary additional technical facilities needed to operate the installation. These may comprise in the area of intake of fresh air 1, the process air treatment, including various filter stages, heating and cooling, 2, an additional sterilizing filter 3, a sterilizable double flap system 4 and in the area of outgoing air once again a sterilizable double flap system 17, a sterilizing filter 16 and the ventilator 15. Also disposed in the technical area are a circulation cleaning station 5 for CIP (cleaning in place) of the installation and various installation components, and an extra pure steam generator 6 for providing sterile steam for sterilizing the installation, the cleaning installation and other components yet to be specified in detail. The installation can be cleaned by the cleaning station 5 in accordance with a cleaning program which is to be specified (parameters are the nature of the cleaning composition(s), cleaning times, temperatures and quantity of the cleaning compositions and of the water used for rinsing and after-rinsing).

Various cleaning nozzles on the installation and in a piping system are actuated via the piping system. The same applies to the sterilization operation, in which saturated steam is admitted both to the installation and to various positions in the piping system. The sterilization takes place in accordance with a formula which is to be set under appropriate autoclaving conditions: after heating the installation to the desired sterilization temperature (e.g. 121°C and 3 bar pressure of saturated steam), a defined holding time is observed for the complete installation and the peripherals to be sterilized, e.g. 20 minutes. After the installation has cooled to, for example, room temperature or a higher process temperature, the then sterilized installation is available for a new process, but it should be noted that the installation must not be opened. The installation tower 9 has special CIP-able metal filters 20 as well as other specific CIP-able design details such as, for example, special aseptic O rings, which are not depicted, and suitable contamination-free port systems 18, 19 for any feed tanks 13 and product collection tanks 11, which are in turn for example steam-sterilizable on their own. The installation tank wall is designed as jacket 7 for heating and cooling and, in some circumstances, with an additional insulation 8. The active ingredient- and polymer-containing solution or suspension is sprayed into the installation via a pump 12, for example a peristaltic pump, from a closed feed tank 10 which derives from the production of active ingredient and polymer. It is also conceivable for the feed tank 10 to remain in the area of polymer and active ingredient production and be connected via a suitable tubing or piping system to the spray pump 12. The installation and the peripheral facilities are operated via an operating terminal 14 which can be installed both in the production area and outside the production area. A possible alternative to the described open production

mode, in which fresh air is drawn via a plurality of filter stages through the installation and, after appropriate treatment of the outgoing air, is returned to the environment, is a closed operating mode in which the incoming and outgoing air sides are connected together by a circulation.

Filling of the granules or pellets once again takes place in a dedicated area. This area can be designed, for example, by isolator technology (fig. 3), so that the product collection tank 11 is connected to a suitable isolator filling unit 21 in the closed state after granule production has taken place. After the contamination-free flap 39 has been opened, the product is screened 22 and, in some circumstances, mixed 23 in a special area. Before it is then metered in the actual unit 24 into the individual containers 32, samples are taken and analyzed 28 within the scope of the described in-process controls. After the individual containers 32 are filled, the containers are closed 26 and leave the filling unit in this state and are then passed to the subsequent production units such as in-process controls within the scope of quality assurance and control and finally to packaging and finishing 27. In a similar way, the empty primary packaging 29 is passed, after it has passed through a washing and rinsing device 30 and been sterilized in a sterilization tunnel 31, to the filling unit 24. Clean room conditions (i.e. above-ambient pressure, particle class 100 and laminar flow conditions) prevail inside the isolator filling unit in each of the treatment steps with open handling of product 33, 34, 35, 36 and 37. Furthermore, there is a defined pressure gradient between these zones 33, 34, 35, 36 and 37 so that no cross-contamination can occur. With an appropriate constructional design it is also possible to dispense with transfer of the product using the collection tank 11. This takes the form of a multi-storey vertical arrangement with the filling unit

installed directly below the granule production installation tower. However, in this case, it is also necessary for granule production to be separated from the filling unit by constructional measures.

Possible formulations may be:

- Mixing of particles or granules which [lacuna] fibrin glue components and active ingredients which may have either hydrophilic, amphiphilic or else lipophilic properties. Release of active ingredient can in these cases also be influenced by formulation additives known from the prior art. It is additionally possible to admix excipients such as, for example, lecithins (egg or soybean lecithin) or else Tween to the particles or granules to improve the wettability. The range of sizes of such powder and granule mixtures can be in a range from 50 to 500 µm or preferably in a range from 50 to 200 µm or else from 200 to 500 µm.

- Mixtures of particles or granules which comprise integrated for example polymer microparticles with additional active ingredients. The polymer may also be polymers not containing fibrinogen or thrombin and of synthetic origin but likewise biodegradable. It is possible to mention as example polymers of lactic acid/glycolic acid (PLGA) or polyanhydrides or polyorthoesters or other suitable polymers known in the prior art. However, protein-based polymers are also possible, such as, for example, albumin. Also suitable are synthetic polymers which are employed as synthetic fibrin glues, such as, for example, poly(octyl cyanoacrylate). The range of sizes of such powder or granule mixtures can be in a range from 50 to 500 µm or preferably in a range from 50 to 200 µm or else from 200 to 500 µm.

- Mixtures of particles or granules which are each composed of an internal core and an external layer.

The external layer comprises fibrin glue components in order to ensure adequate immobilization of the particles or granules in the tissue. The internal core may, on the other hand, also be formed of inert conventional excipients such as, for example, carbohydrates (lactose, mannitol, etc.). It is possible by appropriate choice of the excipients and by appropriate pharmaceutical formulation to influence the solubility of the core in such a way that it is, for example, only slightly soluble and thus brings about a delayed or extended release of active ingredients. The additional active ingredient or active ingredients can be integrated both into the external layer and into the internal core. Suitable examples thereof are crosslinked polymers, for example cellulose derivatives, which are used for example in matrix tablets. The range of sizes of such powder or granule mixtures can be in a range from 50 to 500 µm or preferably in a range from 50 to 200 µm or else from 200 to 500 µm.

- Solids which can be produced by compressing the particle or granule mixture to tablets or else by compaction to compacts (for example roll compaction with subsequent screening (= sizing) to adjust to defined sizes or else briquetting). This results in further degrees of freedom for the pharmaceutical formulation, thus making it additionally possible to alter the release or else making novel administration forms possible. Examples of conceivable modifications according to the prior art are the following: coated tablets, matrix tablets, Oros tablets, components which control release, tablet size and shape. On the other hand, it is possible with compactors to produce from the powder or granules for example lengthy thin strips which could in turn be placed flat directly into a body orifice or an incision after surgical operations. Defined and specific matrix structures of

the fibrin glue components and of the active ingredient components can be constructed both by means of tablets and by means of extrudates. Other conceivable examples are additional stabilizing reticulate fabric structures which can be applied either additionally together with the tablets or with the compacts, thereby making use possible for healing of wounds associated with chronic disease. This makes applications for tissue replacement, for example skin, possible.

- Compact homogeneous micropellets with an average particle diameter of about 50 μm. These may be biodegradable micropellets which do not contain fibrinogen or thrombin (for example albumin, PLGA) and which are coated on the outer surface with a fibrin glue component layer. This exploits the well-known good adhesive properties of the fibrin glue. In addition, at least one therapeutically active substance, or else more than one, is incorporated into the internal biodegradable polymer core. The advantage is that this makes better local administration of the micropellets possible, and they can also be immobilized. It is also possible for the time course of the biodegradability to differ between the layers.

- Compact homogeneous micropellets with an average particle diameter of about 50 μm which comprise a core of fibrin glue components and into which slightly soluble active ingredients are integrated.

- Porous ceramic granules or granules made of materials for bone replacement, such as, for example, calcium phosphates, which are coated with blood plasma proteins, and these coated granules being compressed to a solid. This solid can then be employed as bone replacement. It is also possible in this case to mix

the granules with active ingredients such as antibiotics or growth factors such as, for example, BMP or TGF-β types. One example of BMP is collagen. This can be carried out in such a way that, in a first step, the ceramic granules are coated with a 1st fibrinogen-containing layer. In a 2nd step, thrombin with, for example, growth factors is then applied in a fluidized bed. This can take place as described in DE 198 49 589 C1. The disclosure content is incorporated by reference.

Possible applications of the fibrin glue as carrier system are:

- Topical administration in the same way as conventional fibrin glues for hemostasis in connection with wounds, surgical operations, open body cavities or via mucosal membranes, e.g. mouth, nose, colon or vagina, for local or systemic administration.

- Use as parenteral depot drug form in conjuction with the properties of tolerability, adhesiveness, biodegradability in the form as powder or as granule mixture or else micropellets, without these being dissolved or suspended before administration (for example using special Ject® injection, i.e. needle-free injection of solids).

- Use as parenteral depot drug form in conjunction with the properties of tolerability, adhesiveness, biodegradability as micropellet suspension or of a carrier liquid as dispersion. Suitable examples thereof are oily suspensions (triglycerides, sesame oil). In order to prevent premature coagulation of the suspended micropellets before or during injection, it is possible to add anticoagulants (e.g. trisodium citrate) to the suspension. With polymers

based on fibrin glue components it is necessary in particular to take account of the problems usual with currently available systems for fibrin glues (= spontaneous coagulation through premature contact of the active components fibrinogen and thrombin must be prevented => elaborate preparation etc., see also DE 198 49 589.7 C1).

- Use as carrier system for therapeutic active ingredients by nonparenteral administration (e.g. oral, topical, rectal or vaginal administration).

- Transdermal administration (plaster).

- Use as implant, e.g. as bone replacement or as tissue.

The process for producing powders or granules can preferably be carried out in such a way that the fluidization gas is passed upward through the fluidized bed chamber, and the liquid (solution or suspension) to be dried is sprayed in from the top (top spray), from the bottom (bottom spray) or else from the side (rotor fluidized bed) via a spray system. The fluidization gas has at the same time the task of fluidizing the product present in the fluidizing chamber, introducing the heat necessary to evaporate the spray liquid (water or organic solvent) into the spray stream or the moist product and at the same time taking up and transporting away the evaporated amount of liquid. Discharge of the dried product is prevented on the one hand by choosing a suitable fluidization rate (less than the so-called product discharge rate which can be determined by calculation and experiment), and on the other hand by the product retaining filter which is present in the upper region of the fluidizing chamber and is regularly cleaned, or else by another product separator known from the prior art (such as, for example, a cyclone

separator).

The liquid droplets in a fine mist in the spray cone impinge on the fluidized powdered carrier material and are dried there because of the heat- and matter-transfer conditions which are ideal for fluidized bed processes and which are essentially a consequence of the very large specific surface areas of the particles of the fluidized product. During the spraying there is, for example because of the slow increase in the moisture in the product particle, formation of agglomerates or granules and thus an increase in the particle size.

In the choice of process conditions for thermally labile products (polymers or active ingredients), it must primarily be ensured that they are not harmed by high temperatures. This applies in particular when natural protein-based polymers are processed, especially for natural fibrin glue components (especially for fibrinogen). Suitable incoming air temperatures are, for example, between 15 and 100°C for the product temperature but preferably below 37°C (this particularly applies to fibrinogen). With albumin on the other hand, product temperatures for example of up to 50°C may also be possible without denaturation of the albumin occurring. It must be taken into account in this connection that possible inactivation must always be considered in connection with a particular moisture content, i.e. the thermal stability increases with a decrease in moisture content in the solid product, so that higher temperatures may also acceptable toward the end of the drying.

Another important parameter for assessment of a process is the so-called yield or else recovery of the substance which has been sprayed onto the carrier material. The aim is, of course, to recover virtually

100% of the substance which has been introduced with the spray liquid on the carrier or in the fluidizing chamber. It is true in this connection too that the parameters (e.g. fluidization rate, amount of product precharged, position of the spray nozzle, size and geometries of the apparatus) must and can be selected as suitable, and adapted by experiments, in accordance with the known prior art of fluidized bed technology.

The drying must be carried out to a residual moisture content which is so low that, depending on the chosen storage conditions, no unwanted molecular changes are observed in the polymers or that there is even a marked loss of active ingredient. The residual moisture content for the polymer matrix based on fibrin glue components must be so low that the coagulation reaction does not take place spontaneously. Suitable storage conditions may be: cold storage at 4 to 8°C or ambient conditions (20°C). The granules may additionally be enclosed in a protective atmosphere (e.g. nitrogen or carbon dioxide) and, for example, with exclusion of light. Possible residual moisture contents may then be, for example, between 0.1-5% water content.

Homogeneous active ingredient-containing micropellets of polymers are formed by fibrin glue components or other biodegradable protein or else by biodegradable polymers such as, for example, lactic acid/glycolic acid polymers can, on the other hand, preferably also be produced by direct spraying of a polymer/active ingredient solution or suspension into an empty installation. In this case, the granule nuclei or finely divided particles are produced in situ in the installation and can serve as starter nuclei for further granulation. The installation to be used for this purpose may be, for example, a spray tower or else a fluidized bed installation with a sufficiently free flight path for the sprayed liquid droplets. If

suitable process conditions are complied with, the sprayed liquid droplets can be dried in accordance with the conditions in a spray dryer (but with reduced drying temperatures) in a fluidized bed installation before they, for example, make contact with the container wall in the still moist state and remain stuck there. These fine particles produced in this way are kept in motion and suspension by the fluidizing gas and thus come into contact with the spray mist of the liquid which is subsequently sprayed in and then begin to granulate. It is possible in this way, especially by proceeding very cautiously when starting up the process, to generate a defined granule growth in the originally empty installation. This can be assisted for example by adding known binders. Combination with a classifying discharge of the granules (e.g. through a zigzag classifier and classifying air stream) makes it possible to produce granules with a defined particle size in the installation and to operate the process even in a continuous or quasi continuous manner. The process described herein is essentially based on European patent EP 85103501.4.

It is thus possible to achieve the following physical product properties:

- Particle density: 250-2 000 g/ml, preferably 500-1500 g/ml
- Particle sizes: 20-1 000 µm, preferably 50-500 µm or 30-350 µm
- Particle size distribution: e.g. over- and undersize +/- 50% of the average particle size, preferably +/-25% of the average particle size
- Active ingredient content: 0.1-100%

- Product properties: dust-free, round, cup-shaped particle structure, comparatively high density, no inert cores, no attrition.

The therapeutic active ingredients used can be assigned to the following classes of active ingredients:

Human uses:

- antibiotics
- corticosteroids
- antimycotics
- neuroleptics
- antiepileptics
- steroid hormones
- anticancer hormones
- substances which promote wound healing
- cytostatics
- immunomodulators
- anesthetics, analgesics
- peptide hormones (replacement therapy)
- antirheumatics
- vaccines, antibodies
- monoclonal antibodies
- amino acid sequences (DNA, peptides, proteins) => gene therapy
- biological cells (gene therapy)
- biotechnologically produced growth factors, cells (tissue growth factors)

Veterinary medicine:

- hormones
- antibiotics
- insecticides, anthelmintics
- vaccines, antibodies

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GLATT PROCESS TECHNOLOGY GMBH

Claims

1. A biodegradable depot medicament formulation comprising a carrier system composed of biodegradable blood plasma proteins which have been dried by fluidized bed drying with retention of their properties, and an active ingredient which is to be administered as depot or an active ingredient combination, where the blood plasma protein is selected from thrombin and fibrinogen, albumin or mixtures thereof and that the carrier system is in the form of microporous granules with a particle size of from 20 to 500 µm.

2. A depot medicament formulation as claimed in claim 1, characterized in that the carrier system is a solid which has been produced by compression of the granules.

3. A depot medicament formulation as claimed in claim 1 or 2, characterized in that it is in the form of a granule mixture of particles of the carrier system and of the active ingredient to be administered as depot or of an active ingredient combination thereof.

4. A depot medicament formulation as claimed in claim 1 or 2, characterized in that it is in the form of mixed granules of the biodegradable blood plasma protein and of the active ingredient or of the active ingredient combination thereof.

5. A depot medicament formulation as claimed in claim 1 or 3, characterized in that it is composed of mixtures of particles or granules which are formed of an internal core and an external layer, where the external layer has been formed by blood plasma

proteins, and the internal core is composed of an inert excipient.

6. A depot medicament formulation as claimed in claim 5, characterized in that the internal core has been formed from carbohydrates, in particular lactose or mannitol.

7. A depot medicament formulation as claimed in claim 1 or 2, characterized in that it is in the form of compact homogeneous micropellets with an average particle diameter of from 35 to 500 µm, preferably 50 to 150 µm.

8. A depot medicament formulation as claimed in at least one of claims 1 to 7, characterized in that it is composed of ceramic granules and/or calcium phosphates which have been compressed together to give a shaped article and which have been coated with a blood plasma protein.

9. A depot medicament formulation as claimed in claim 8, characterized in that the blood plasma protein comprises antibiotics and/or growth factors.

10. A depot medicament formulation as claimed in at least one of claims 1 to 9, characterized in that the active ingredient or the active ingredient combination is selected from antibiotics, corticosteroids, antimycotics, neuroleptics, antiepileptics, steroid hormones, anticancer hormones, substances which promote wound healing, cytostatics, immunomodulators, anesthetics, analgesics, peptide hormones (replacement therapy), antirheumatics, vaccines, antibodies, monoclonal antibodies, amino acid sequences (DNA, peptides, proteins), gene therapy, biological cells, biotechnologically produced growth factors, cells.

11. A depot medicament formulation as claimed in at least one of claims 1 to 7, characterized in that it is employed for topical administration.

12. A depot medicament formulation as claimed in at least one of claims 1 to 7, characterized in that it is employed for parenteral administration.

13. A depot medicament formulation as claimed in at least one of claims 1 to 7, characterized in that it is employed for transdermal administration (plaster).

14. A depot medicament formulation as claimed in claim 8 or 9, characterized in that it is employed as implant such as bone replacement.

15. A process for producing the depot medicament formulation as claimed in at least one of claims 1 to 9, characterized in that the biodegradable blood plasma protein is sprayed in the form of a solution and/or suspension into a fluidized bed installation and dried under mild conditions with retention of the properties.

AMENDED SHEET

Abstract

The invention relates to a biodegradable depot medicament formulation comprising a carrier system composed of biodegradable blood plasma proteins which have been dried by fluidized bed drying with retention of their properties, and an active ingredient which is to be administered as depot or an active ingredient combination.

Fig. 1

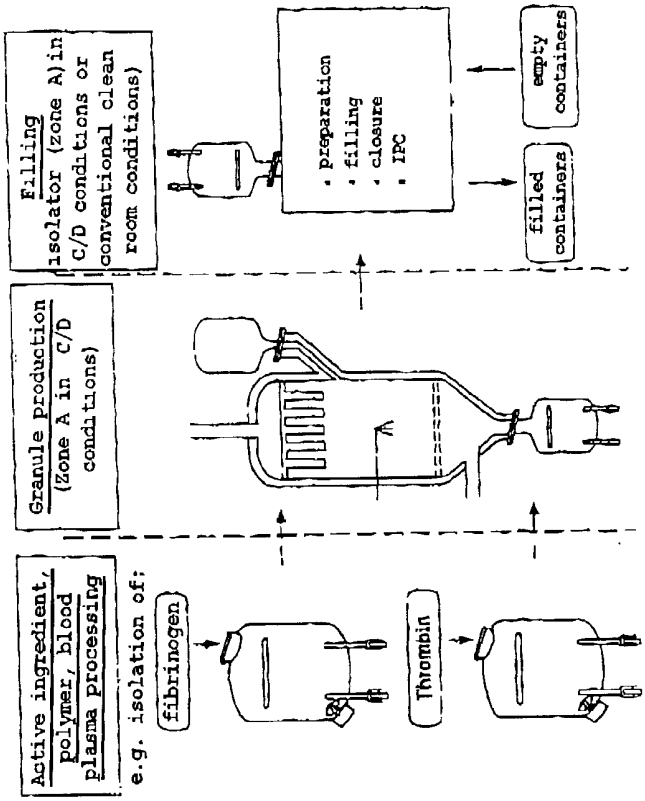
Active ingredient, polymer, blood plasma processing
e.g. isolation of:
fibrinogen
Thrombin
Granule production (Zone A in C/D conditions)
Filling isolator (zone A) in C/D conditions or conventional clean room conditions)
. preparation
. filling
. closure
. IPC
empty containers
filled containers

Fig. 1

Fig. 2

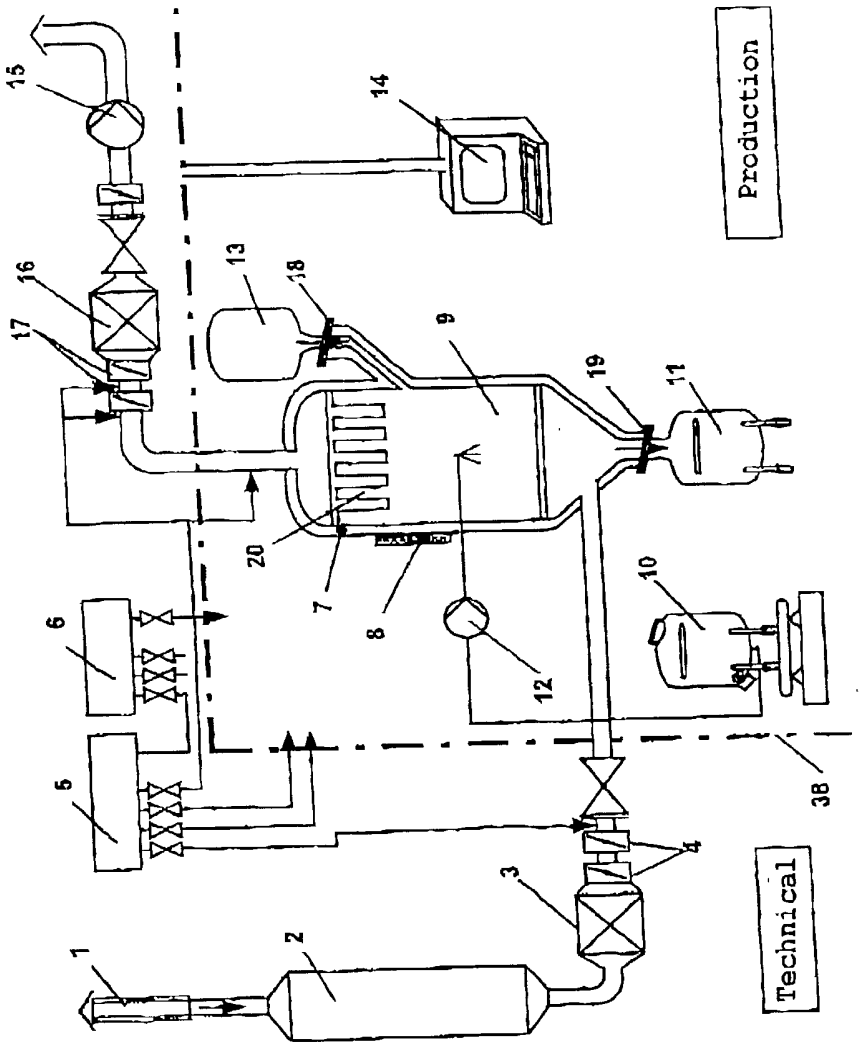

Fig. 2

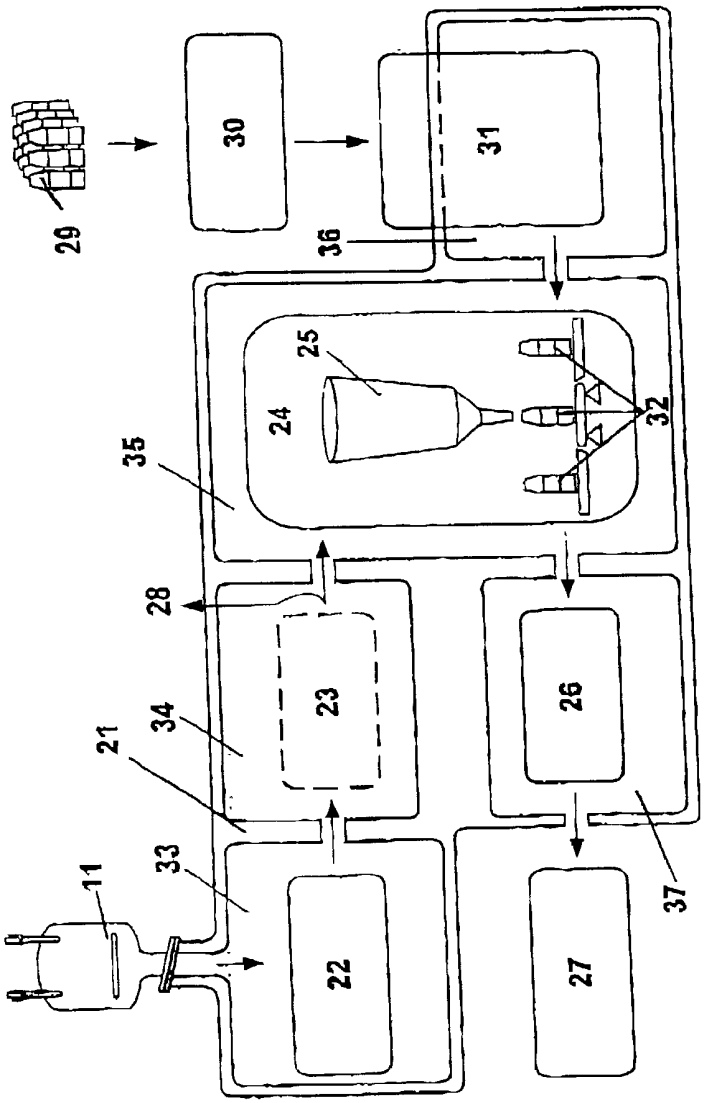

Fig. 3

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY

(Includes Reference to PCT International Applications)

ATTORNEY DOCKET NUMBER
3671/0K437

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed for and which a patent is sought on the invention entitled:

BIODEGRADABLE EXCIPIENT SYSTEMS FOR THERAPEUTICALLY ACTIVE SUBSTANCES AND METHOD FOR PRODUCING THE SAME

the specification of which (check only one item below):

[] is attached hereto.

[] was filed as United States application

Serial No. _____

on _____

and was amended

on _____ (if applicable).

[X] was filed as PCT international application

Number PCT/EP00/09558

on September 29, 2000

and was amended under PCT Article 19

on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

COUNTRY (if PCT indicate PCT)	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 U.S.C. 119
Germany	199 47 354.4	October 1, 1999	[X] YES []NO
			[] YES [] NO
			[] YES [] NO
			[] YES [] NO

Combined Declaration for Patent Application and Power of Attorney (Continued) (Includes Reference to PCT International Applications)	ATTY'S DOCKET NUMBER 3671/0K437

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. 120:

U.S. APPLICATIONS		STATUS (Check one)		
U.S APPLICATION NUMBER	U.S. FILING DATE	PATENTED	PENDING	ABANDONED

PCT APPLICATIONS DESIGNATING THE U.S.					
PCT APPLICATION NO	PCT FILING DATE	U S SERIAL NUMBER ASSIGNED (if any)			
PCT/EP00/09558	9/29/00				

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agents to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. Michael J. Sweedler #19,937, S. Peter Ludwig #25,351, Paul Fields #20,298, Joseph B. Lerch #26,936, Melvin C. Garner #26,272, Ethan Horwitz #27,646, Adda C. Gogoris #29,714, Bert J. Lewen 19,407, Henry Sternberg #22,408, Peter C. Schechter #31,662, Robert Schaffer #31,194, Robert C. Sullivan, Jr. #30,499, Joseph R. Robinson #33,448, Paul F. Fehlner #35,135, Scott G. Lindvall #40,325, David Leason #36,195 and Pierre R. Yanney #35,418, Irina E. Vainberg #48,008

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200	FULL NAME OF INVENTOR	FAMILY NAME LUY	FIRST GIVEN NAME Bernhard	SECOND GIVEN NAME
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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patents issuing thereon.

SIGNATURE OF INVENTOR 201	SIGNATURE OF INVENTOR 202	
DATE 6.6.02	DATE 6.6.2002	